Long-Term Survival Following Aortic Valve Replacement: The Influence of Age, Prosthesis-Patient Mismatch and Indexed Effective Orifice Area

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Highlights

Background

Prosthesis-patient mismatch (PPM) has been linked to reduced long-term survival after aortic valve replacement. We studied the influence of age, PPM and indexed effective orifice area (iEOA) in this setting.

Methods

Patients (n=586) subjected to aortic valve replacement were followed up for a mean of 7.8 (maximum 20) years. The study population was divided into four equivalent groups by age. Mortality data was extracted from the National Statistics database. Data pertaining to patient body surface area and valve effective orifice area was collected prospectively and mismatch (moderate or severe) was defined according to established values. The Cox proportional hazard model was used to study the effect of age, mismatch and iEOA on survival. The Log Rank test was used to compare survival curves by age groups and date of surgery.

Results

The incidence of moderate PPM was 24.6%, and of severe PPM 3.9%. Mismatch increased the hazard of death by 31.2% for moderate PPM and 70.3% for severe PPM but did not reach statistical significance. Mean age of patients with mismatch (n=167) was 2.52 years less than in those without (63.35±10.61 versus 65.87±11.69, p=0.016). Age significantly affected survival, increasing the risk of death by 7.3% for every incremental year. Mean iEOA was 0.94±0.15cm2/m2; for every 0.1unit increase in iEOA the risk of death decreased by 8.8%.

Conclusions

Long-term survival was significantly affected by age at operation. Although mismatch increased hazard of death the effect did not reach statistical significance. A larger iEOA had a significant beneficial effect on survival.

Keywords: long-term survival; aortic valve replacement; age; prosthesis-patient mismatch; indexed effective orifice area

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Introduction

The concept of prosthesis-patient mismatch was introduced in 1978.[1] PPM occurs when the effective orifice area (EOA) of a prosthesis is too small for the patient's body size, resulting in excessively high postoperative valve gradients.[2] Independent researchers evaluating valve performance in vivo by echocardiography have underlined the overestimation of EOA in tables[3,4] issued by valve manufacturers (based on in-vitro testing)[5,6] and this has resulted in revised valve specifications.[7]

Valve design has evolved from intra-annular implantation where the internal orifice diameter is smaller than the tissue annular diameter (TAD) to the introduction of supra-annular implantation where these diameters are equivalent.[8] This feature allows for

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supra-annular implantation of a larger valve for a fixed TAD, often of the magnitude of one valve size. Various additional design features such as the TopHat design,[4] a lower-profile sewing ring and external mounting of pericardial tissue contribute to a larger EOA.[9]

The improvements in EOA are based on the premise that inferior haemodynamics result in suboptimal clinical outcomes. Studies have linked PPM with persistent left ventricular hypertrophy, diastolic dysfunction and curtailed functional improvement.[10] Late cardiac complications [11] and accelerated degeneration of bioprostheses have also been reported.[12] However, in the setting of advancing age, the combined effects of these factors on survival remains unclear.[13,14]

Although age undoubtedly increases early and late mortality after aortic valve replacement, the direct effect of mismatch remains debatable.[15-17] We studied the effect of the interaction of age and mismatch as well as the influence of iEOA on long-term survival both as a continuous variable, and as a categorical determinant of moderate or severe PPM.

Methods

586 consecutive patients (61.6% male, mean age 63.6±12.0) undergoing AVR ±CABG between January 1995 and December 2016 in a single-surgeon's practice were enrolled in the study and grouped according to age: 15-59 (n=148), 60-67 (n=145), 68-74 (n=149), 74 or more (n=144). Patients were excluded if they underwent transcatheter valve implantation or other procedures. Baseline patient characteristics as well as postoperative complications were recorded in the presence or absence of PPM (table 1). Mortality data was obtained from the National Statistics database. Patients were followed up for a mean of 7.8 years (median 7.3) up to a maximum of 20 years. The Hospital Scientific Ethical Committee waived the necessity for consent as the study was retrospective and patient data was anonymized. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Surgery was performed in a standard fashion under normothermic bypass with antegrade cold cardioplegia. We used the internal thoracic artery supplemented by saphenous vein grafts when additional coronary bypass was necessary. No patient included in this series underwent root enlargement. Ninety three percent of patients below 70 received a mechanical valve whereas 96% of patients over 70 received a bioprosthesis. The choice of valves implanted evolved with the introduction of models with a larger EOA, potentially providing superior haemodynamics (table 2).

No PPM was defined as an indexed effective orifice area (iEOA) of >0.85cm^2/m^2, moderate PPM as 0.65-0.85cm^2/m^2 and severe as <0.65cm^2/m^2, and was calculated according to published data on valve EOA derived from independent researchers' post-operative echocardiographic studies (table 3).

Statistical Methods

The student's t-test was used to compare age groups with or without PPM. The Cox proportional hazard model was used to study the impact of age, iEOA and PPM category on long-term survival. Survival analysis was performed using the facilities of the Statistical Package for Social Sciences (SPSS, Inc, Chicago, IL) by using both a non-parametric approach (Kaplan-Meier estimates) and semi-parametric approach (Cox regression analysis). The Log-Rank (Mantel-Cox) test was used to determine whether the Kaplan Meier survival curves for different age-groups differed significantly at the 0.05 level.

Table 1. Baseline patient characteristics and postoperative complications

parameter	No PPM	Yes PPM	p value
n	419	167	
age	65.87±11.69	63.35±10.61	0.016
female	155 (36.9%)	72 (42.9%)	0.180
urgent surgery	48 (11.4%)	21 (12.5%)	0.715
concomitant CABG	139 (33.1%)	59 (35.1%)	0.639
ejection fraction (%)	70.44±14.31	69.71±13.59	0.717
mean Parsonnet score	13.96±7.17	13.40±6.61	0.375
mean EuroScore	5.31±2.07	4.87±1.99	0.037
mean logistic EuroScore	5.02±3.94	4.26±3.00	0.046
mean hospital stay (survivors)	6.20±3.62	6.30±4.87	0.797
median ventilation time (hours)	8	7	0.387
patients transfused	118 (28.1%)	53 (31.5%)	0.405
mean transfusion volume (units)	1.26±2.41	1.11±2.20	0.576
mean haemorrhage volume (ml)	459.8±311.0	476.4±348.1	0.617
IABP usage	18 (4.3%)	4 (2.4%)	0.272
>24 hours inotropic support	116 (27.6%)	43 (25.6%)	0.618
atrial fibrillation/flutter	97 (23.1%)	47 (28.0%)	0.214

Table 2. Valves implanted during the study period

valve size	1995-2001*	2002-2015**
mechanical 19, 21	CarboMedics Reduced	CarboMedics TopHat
23	CarboMedics Standard	CarboMedics TopHat
25	CarboMedics Standard	CarboMedics Standard
bioprosthetic 19, 21, 23	Carpentier Edwards Perimount	Sorin Mitroflow
25	Carpentier Edwards Perimount	Carpentier Edwards Perimount/Magna

*11 St Jude Medical Toronto SPV valves inserted during this period
**7 Perceval valves inserted during this period

Results

Baseline characteristics and postoperative complications in patients without or with PPM did not differ, except for logistic/EuroSCORE risk, which was affected by age (table 1).

Table 3. EOA values

valve model	size19 EOA	size 21 EOA	size 23 EOA	size 25 EOA	reference source*
CarboMedics	1.0	1.54	1.63	1.98	[18,19]
Carpentier Edwards	1.1	1.5	1.8	1.8	[13,20,21]
Sorin Mitroflow	1.2	1.5	1.8	2.3	[13,22,23,24]
St Jude Medical Toronto SPV		1.3	1.5	1.7	[25]

*reference source refers to the publications quoting the EOA values used in this study

412 of 586 patients were alive at the completion of the study. The survival curves display the Kaplan-Meier survival probabilities for each age group against survival duration (figure 1). The log-rank test show that the Kaplan Meier survival curves of the four age-groups differ significantly when compared pairwise (table 4).

Survival was also plotted and analysed in relation to operative date, in five-year quartiles (figure 2). There was no influence on survival and the incidence of PPM within these quartiles was similar (p = 0.965) (table 5).

140 patients received a size 25 valve, 202 patients received a size 23, 195 patients received a size 21, and 49 patients received a size 19 valve. The incidence of moderate PPM was 24.6% and severe PPM was 3.9% (figure 3). Mismatch was present in 167 patients and was more prevalent in younger patients. In fact, the mean age of patients with mismatch (63.35±10.61) was 2.52 years lower than their counterparts with no mismatch (65.87±11.69) and this difference is significant (p=0.016) (figure 4).

There was no correlation between PPM and perioperative mortality. There were 11 early deaths (1.9%), and of these, 10 patients had no PPM and one had moderate PPM. Seven patients who died underwent concomitant coronary grafting and 8 were over 70 years old, both recognized risk factors for increased perioperative mortality.

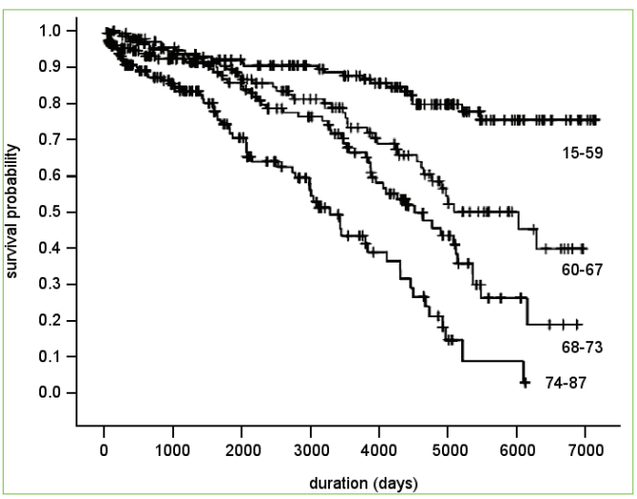

Figure 1. Kaplan-Meier survival curves for the four age groups

Table 4. Log-Rank (Mantel-Cox) test relating survival time to age

age groups	Chi-Square	df	p value
group 1 versus group 2	11.607	1	0.001
group 1 versus group 3	30.722	1	0.000
group 1 versus group 4	66.560	1	0.000
group 2 versus group 3	4.360	1	0.037
group 2 versus group 4	28.157	1	0.000
group 3 versus group 4	13.345	1	0.000
four groups collectively	80.057	3	0.000

df: degrees of freedom

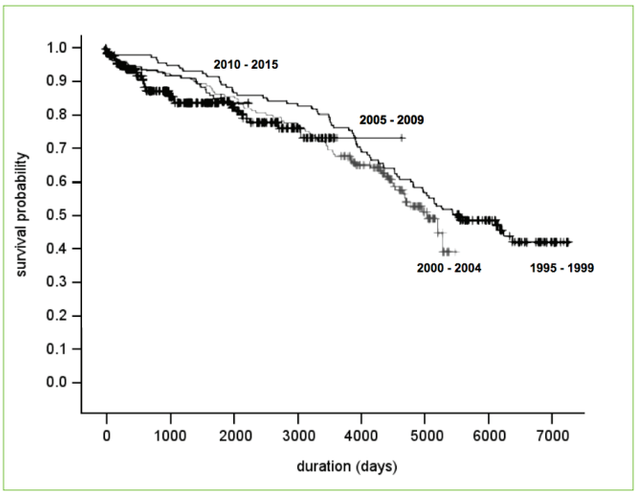

Figure 2. Kaplan-Meier survival curves versus date of surgery (in five-year quartiles)

Table 5. PPM incidence in five-year quartiles

period	No PPM	Yes PPM
1995-1999	89	37
	70.6%	29.4%
2000-2004	117	49
	70.5%	29.5%
2005-2009	93	36
	72.1%	27.9%
2010-2015	120	45
	72.7%	27.3%
total	419	167
	71.5%	28.5%

X2(3) = 0.275, p = 0.965

Survival probability was significantly affected by patient's age with the hazard of dying increasing by around 7.3% for every incremental year. In patients with severe and moderate mismatch the hazards of dying were respectively 70.3% and 31.2% higher compared to patients with no PPM, but the increase was not statistically significant. In patients with mismatch the hazards of dying were 86.5% higher for 19mm valves, 68.7% for 21mm valves and 13.7% for 23mm valves compared to 25mm valves. These hazard ratios are not significant mainly because the incidence of mismatch was low, particularly for the larger valves. (table 6).

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Table 6. Cox regression relating survival time to age and PPM

	parameter estimate	SE	Wald test	p value	Hazard Ratio	95% lower	CI higher
age	0.0701	0.0092	58.06	0.000	1.073	1.053	1.092
severe PPM	0.5324	0.3251	2.682	0.101	1.703	0.901	3.221
moderate PPM	0.2715	0.2073	1.715	0.190	1.312	0.874	1.969
no PPM	0				1		
size 19 PPM	0.6234	0.3584	3.026	0.082	1.865	0.924	3.765
size 21 PPM	0.5232	0.3143	2.771	0.096	1.687	0.911	3.124
size 23 PPM	0.1287	0.2927	0.193	0.660	1.137	0.641	2.019
size 25 PPM	0				1		

SE: standard error, CI confidence interval

Mean iEOA was 0.94±0.15cm²/m². When iEOA was analysed as a continuous parameter rather than a categorical parameter, a higher iEOA was associated with a significantly reduced hazard ratio of dying. The chance of survival increased by 8.8% for every 0.1 unit increment in iEOA (table 7).

In conclusion, age was a significant predictor of long-term survival whereas prosthesis-patient mismatch failed to exert a statistically significant effect. This situation applied for both moderate and severe mismatch and for all valve sizes used. In contrast long-term survival was affected by iEOA when this was analyzed as a continuous variable.

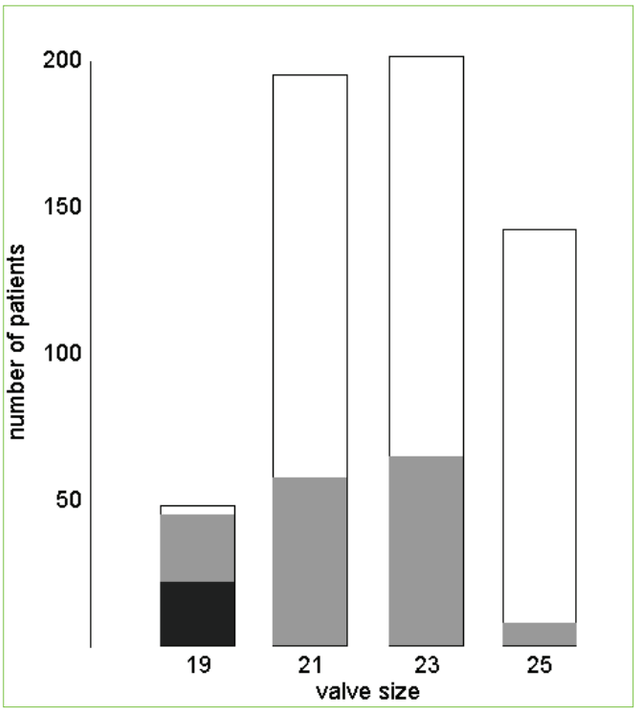

Figure 3. Distribution of PPM by severity: gray moderate, black severe

Table 7. Cox regression relating survival time to age and iEOA:

	parameter estimate	SE	Wald test	df	p value	Hazard Ratio	95% lower	CI higher
age	0.0683	0.0082	69.38	1	0.000	1.071	1.054	1.088
iEOA	-0.0921	0.0312	8.714	1	0.003	0.912	0.858	0.970

Wald test: used to test the true value of the parameter, based on the sample estimate df: degrees of freedom associated with each parameter estimate

Discussion

Cardiac-related mortality was shown to be increased by prosthesis-patient mismatch in a meta-analysis of 34 observational studies published in 2012.[26] This analysis included a number of studies that failed to demonstrate a significant effect of PPM, amongst which were one study [27] with a longer mean follow-up (9.1 vs. 7.8 years) and a second [28] with a comparable follow-up (median of 7.3 vs. 7.3 years) to our study. Both these studies failed to show a significant effect on survival, raising the possibility that a longer follow-up may be salient. The authors stressed the value of preventing PPM, particularly in younger patients in whom long-term survival may be impacted to a greater extent.

The incidence of common postoperative complications was similar in patients with or without PPM. Certain complications have been shown, by multivariate analysis, to affect long-term outcome. [29] In this study risk stratification was higher by logistic (p=0.046) and additive EuroSCORE (p=0.037) in patients without PPM because this group was older by 2.52 years, age being a contributor to the score. The incidence of mismatch is higher in younger patients and this may attenuate its effect on survival. Follow-up duration is inversely proportional to advancing age at operation. Studies with a longer follow-up have failed to demonstrate a deleterious effect of mismatch. The combined effect of a younger age and a longer follow-up may overshadow the importance of mismatch in determining long-term survival. Although mismatch leads to adverse cardiac events its effect on survival is reduced by advancing age.[29] Our results suggest that age, and its direct effect on follow-up duration, significantly affects survival whereas mismatch does not.

A long follow-up necessarily entails evolving practices including the implantation of novel valves that may significantly affect survival. Analysis of survival by operative date, in four five-year quartiles, showed no significant difference in survival in these groups.

When valve haemodynamics are translated into a continuum of iEOA a significant effect on long-term survival becomes evident. This relationship failed to reach statistical significance with mismatch because of the low incidence of moderate PPM, and the very low incidence of severe PPM. All data pertaining to valve EOA was obtained from published studies and not from our own post-operative measurements. These values should be readily available in theatre and act as a guide to the surgeon implanting an aortic prosthesis with the goal of avoiding mismatch. Our study suggests that the largest size valve with the best possible EOA should always be implanted. In extreme circumstances of a small aortic root, enlargement may be performed. However, the increased operative risk of this procedure has not been shown to benefit long-term survival.[30]

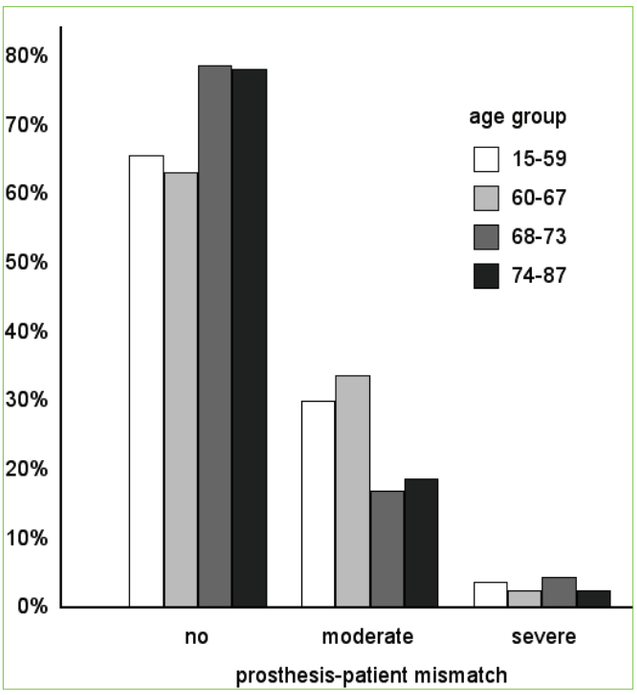

Figure 4. Distribution of PPM by age

Limitations

The data was derived from a single surgeon's practice and may not be representative of a wider population. A change in the use of certain valve models during the study period may have influenced the outcome. The low incidence of mismatch may have been a factor limiting statistical significance.

Conclusion

PPM, whether moderate or severe, did not significantly curtail long-term survival. A larger iEOA increased survival by 8.8% per 0.1 unit increase. Age exerted a significant effect on survival, reducing it by 7.3% for each incremental year.

Declarations of interests

The authors declare no conflict of interest.

Acknowledgements

The authors agree to abide by the requirements of the "Statement of publishing ethics of the International Cardiovascular Forum Journal.[31]

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